Health Technical Services Project

Discussion Papers on HIV/AIDS Care and Support

Preventing Opportunistic Infections in Human Immunodeficiency Virus–Infected Persons: Implications for the Developing World

Prepared by
Jonathan E. Kaplan, Dale J. Hu, K. Holmes,
Harold W. Jaffe, Henry Masur, and Kevin M. DeCock

Discussion Paper Number 4

June 1998

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UNITED STATES AGENCY FOR INTERNATIONAL DEVELOPMENT

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About HTS

The Health Technical Services Project provides short- and medium-term technical assistance to USAID — specifically, to regional bureaus, regional and country missions, and the Office of Health and Nutrition in the Center for Population, Health and Nutrition of the Bureau for Global Programs, Field Support, and Research (G/PHN/HN). This technical assistance supports USAID programs in maternal and child health, nutrition, health policy reform, HIV/AIDS, and environmental health. HTS activities are concentrated in three broad technical areas: project design, policy and strategy, and evaluation and monitoring.

HTS's work is grounded in the four complementary values that guide USAID's efforts to reengineer its operations:

a customer focus
participation and teamwork
empowerment and accountability
management for results.

Foreword

The U.S. Agency for International Development seeks to develop and promote effective strategies for providing basic care and support to those affected by HIV/AIDS. This series of Discussion Papers on HIV/AIDS Care and Support represents a first step in this effort.

HIV/AIDS care and support mitigate the effects of the pandemic on individuals, families, communities, and nations. Such interventions are an important component of the overall response to HIV/AIDS because they increase the impact of prevention strategies and mitigate the negative consequences of the epidemic on the prospects for sustainable development.

This series of Discussion Papers covers several key issues related to care and support:

- Human rights and HIV/AIDS
- Palliative care for HIV/AIDS in less developed countries
- Preventing opportunistic infections in people infected with HIV
- Psychosocial support for people living with HIV/AIDS
- Community-based economic support for households affected by HIV/AIDS
- Responding to the needs of children orphaned by HIV/AIDS
- Systems for delivering HIV/AIDS care and support.

Each paper provides a preliminary review of some of the current thinking and research on these broad and complex topics. It is important to note that the papers are not meant to be comprehensive — time and resource constraints prevented the authors from reviewing all the relevant literature and from contacting all the people who have valuable experience in these and related fields. Nor have they been subject to technical or peer review. Their purpose is to stimulate a broad conversation on HIV/AIDS care that can help USAID define its future program activities in this area. We welcome your participation in this process.

Two additional papers on the topic of voluntary counseling and testing were prepared with USAID support:

The Cost Effectiveness of HIV Counseling and Testing

Voluntary HIV Counseling and Testing Efficacy Study: Final Report

These two papers are available from the IMPACT Project, Family Health International, 2101 Wilson Boulevard, Suite 700, Arlington, VA 22201; www.fhi.org.

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—Linda Sanei, Technical and Program Advisor,
Health Technical Services Project

Contents

LIST OF TABLES AND FIGURES

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PREVENTING OPPORTUNISTIC INFECTIONS IN HUMAN IMMUNODEFICIENCY VIRUS–INFECTED PERSONS: IMPLICATIONS FOR THE DEVELOPING WORLD

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Abstract. More than 18 million persons in the world are estimated to have been infected with human immunodeficiency virus (HIV), the cause of the acquired immunodeficiency syndrome (AIDS). As immunodeficiency progresses, these persons become susceptible to a wide variety of opportunistic infections (OIs) The spectrum of OIs varies among regions of the world. Tuberculosis is the most common serious OI in sub-Saharan Africa and is also more common in Latin America and in Asia than in the United States. Bacterial and parasitic infections are prevalent in Africa; protozoal infections such as toxoplasmosis, cryptosporidiosis, and isosporiasis are also common in Latin America. Fungal infections, including cryptococcosis and *Penicillium marneffei* infection, appear to be prevalent in Southeast Asia. Despite limited health resources in these regions, some measures that are recommended to prevent OIs in the United States may be useful for prolonging and improving the quality of life of HIV-infected persons. These include trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia, toxoplasmosis, and bacterial infections; isoniazid to prevent tuberculosis; and 23-valent pneumococcal vaccine to prevent disease due to *Streptococcus pneumoniae*. Research is needed to determine the spectrum of OIs and the efficacy of various prevention measures in resource-poor nations, and health officials need to determine a minimum standard of care for HIV-infected persons. An increasing problem in the developing world, HIV/AIDS should receive attention comparable to other tropical diseases.

More than 18 million persons in the world are estimated to have been infected with human immunodeficiency virus (HIV), the cause of the acquired immunodeficiency syndrome (AIDS) (Figure 1).[1] In the later stages of HIV infection, as immunodeficiency progresses, HIV-infected persons become susceptible to a variety of opportunistic infections (OIs). We have defined OIs as infections that occur with greater frequency or severity in HIV-infected persons, presumably because of immunosuppression.[2]

With the rapid global spread of HIV and AIDS, a plethora of OIs have been reported from various regions of the world. In a recent review, more than 100 pathogens–viruses, bacteria, fungi, protozoa, helminths, and arthropods–were identified as having caused opportunistic disease in HIV-infected persons.[2] A relatively small percentage of these pathogens cause the majority of infections, but their impact on the health of HIV-infected persons is enormous.

In July 1995, agencies of the United States Public Health Service (USPHS), in collaboration with the Infectious Diseases Society of America (IDSA), published guidelines for preventing opportunistic infections in HIV-infected persons.[2–4] These guidelines, written for health care providers, were intended for use primarily in North America. They address 17 OIs, selected because of their high incidence, associated morbidity, and mortality, or because they offer particular opportunities for prevention. Each OI was approached from the standpoint of prevention of exposure to the pathogen, prevention of first episode of disease by chemoprophylaxis or vaccination, and prevention of disease recurrence. Disease incidence and severity; the feasibility, efficacy, and cost of chemoprophylaxis; drug toxicities and interactions; and the impact of the prevention measure on quality of life were all considered in developing the prevention recommendations. The recommendations were rated according to their strength and to the quality of evidence supporting their use.[2]

Publication and dissemination of the USPHS/IDSA guidelines have raised questions concerning the applicability of the guidelines to other regions of the world. In industrialized regions such as Western Europe, Canada, Australia, New Zealand, and Japan, where the spectrum of OIs and prevention options and priorities are probably similar to those in the United States, the USPHS/IDSA guidelines are likely to be highly applicable. However, their applicability in developing countries in sub-Saharan Africa, Central and South America, and Asia, regions in which the prevalence of HIV infection and AIDS is already high or is increasing rapidly, is unclear. In these regions, the spectrum of OIs, the range of prevention options, and the susceptibility of OI pathogens to antimicrobials may differ from those in North America. Additionally, prevention options and priorities can be expected to differ greatly, depending on the availability of health resources. For example, a chemoprophylaxis regimen widely affordable in North America may be unaffordable for most individuals in a country with a low per capita expenditure on health care. Customs and behaviors that might influence adherence to preventive measures will also differ markedly from one region to another; these cultural factors may be particularly important to consider when assessing the usefulness of chemoprophylaxis.

Despite these differences, some of the prevention measures recommended in the United States may have great potential for reducing the impact of OIs in HIV-infected persons in the developing world. These include trimethoprim-sulfamethoxazole (TMP/SMX) for *Pneumocystis carinii*

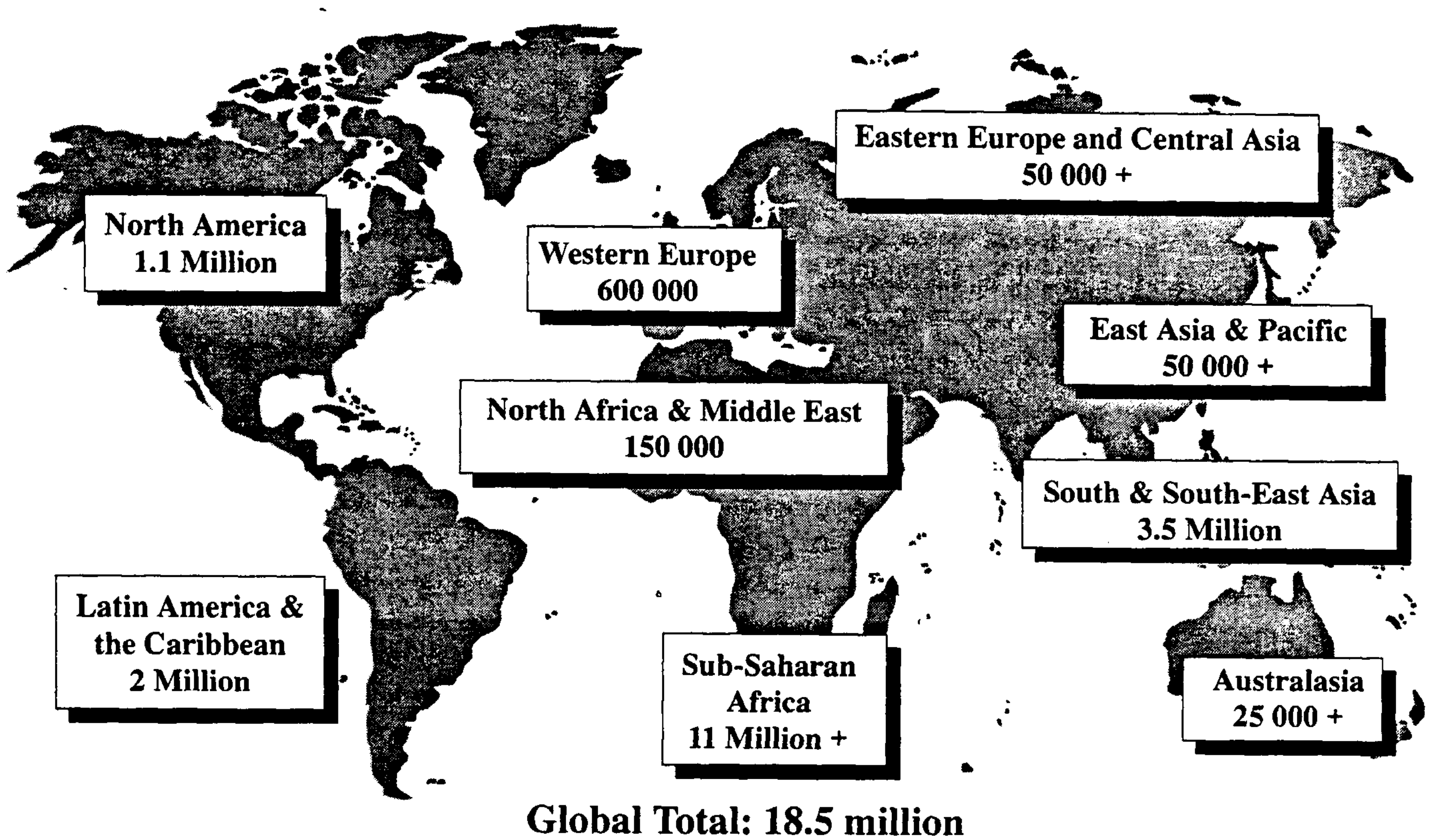

FIGURE 1. Estimated distribution of total adult human immunodeficiency virus infections from the late 1970s/early 1980s until mid-1995.[1]

pneumonia (PCP), cerebral toxoplasmosis, and various bacterial infections; isoniazid (INH) for tuberculosis (TB); and 23-valent pneumococcal vaccine for disease due to *Streptococcus pneumoniae.*

In this article, we explore the OIs of importance in developing countries in the regions of the world that have been most affected by the HIV pandemic, discuss prevention measures that may reduce the impact of OIs, and suggest research priorities for reducing the impact of OIs in these areas. We also promote the concept that like malaria, schistosomiasis, filariasis, and other tropical diseases that most often occupy the pages of the *American Journal of Tropical Medicine and Hygiene,* HIV/AIDS merits the attention of epidemiologists, researchers, and public health officials who are concerned about diseases in the tropical world.

OPPORTUNISTIC INFECTIONS OF IMPORTANCE IN DIFFERENT REGIONS OF THE WORLD

The spectrum of OIs associated with HIV infection differs considerably in various regions of the world. Although the reasons for the differences are not completely understood, they are likely to include the prevalence of OI pathogens in the environment, behaviors and ecologic factors that result in exposure to these pathogens, and other undefined factors.

Determining the spectrum of OIs in a given region requires surveillance systems and diagnostic services that are frequently absent or weak in many developing countries. Depending on the availability of resources, the accessibility of patients, and the interests of local investigators, surveillance systems may sample only certain subgroups of AIDS patients or only patients at certain stages of disease (e.g., terminal stage as in autopsy studies).

Diagnostic services are often insufficient to diagnose OIs correctly. Opportunistic infections that can be diagnosed with reasonable accuracy by physical examination (e.g., oral candidiasis) or by inexpensive laboratory techniques (e.g., india ink stain of cerebrospinal fluid to identify *Cryptococcus neoformans*) may be documented more frequently than OIs requiring more expensive diagnostic technology, such as PCP, disseminated *Mycobacterium avium* complex (MAC) infection, or cytomegalovirus (CMV) disease. While diagnostic limitations generally result in underdiagnosis of conditions, they may also result in overdiagnosis of some OIs. For example, patients with acid fast smear-negative pulmonary disease that cannot be investigated more fully may have TB falsely diagnosed. Biases in diagnosing and reporting OIs may be especially important among socially disadvantaged groups with limited access to diagnostic and health care services. Finally, differences in clinical definitions make comparisons between published reports difficult. For all these reasons, much less is known about the frequencies of different OIs in the developing world than in industrialized countries.

Because few cohort studies in resource-poor countries have included monitoring of immunologic status, little information is available in these settings on the natural history of HIV disease, including the chronological order and the stages of immune deficiency at which different OIs occur. There is a widespread belief that HIV disease progresses more rapidly in sub-Saharan Africa than in industrialized countries.[5] However, an apparently rapid course could reflect

TABLE 1

Organisms recovered from blood cultures from human immunodeficiency virus–infected patients hospitalized in Nairobi, Kenya, and Abidjan, Cote d'Ivoire*

Organism	Percentage of patients from whom organism was isolated	
	Nairobi[15]	Abidjan[16]
Non-typhoid *Salmonella*	10.5%	7.9%
Streptococcus pneumoniae	7.4%	1.5%
Mycobacterium tuberculosis	NA	4.0%
Cryptococcus neoformans	1.1%	2.5%

* Blood cultures were positive in a total of 26% of patients in Nairobi and 17% in Abidjan. Only the most common organisms isolated are listed. NA = not available.

TABLE 2

Prevalence of opportunistic infections among persons dying with human immunodeficiency virus disease in Abidjan, Cote d'Ivoire[18]

	Prevalence (%)	Cause of death (%)
Tuberculosis	38%	32%
Bacteremia	16%	11%
Toxoplasmosis, central nervous system	15%	10%
Pyogenic pneumonia	30%	8%
Purulent meningitis	5%	5%
Nonspecific enteritis	10%	3%
Cryptococcosis	3%	2%
Pneumocystis carinii pneumonia	3%	2%
Nocardiosis	4%	2%
Non-Hodgkin's lymphoma	3%	2%
Kaposi's sarcoma	9%	2%
Cytomegalovirus disease	18%	2%

initial diagnosis of HIV/AIDS late in the course of infection, greater exposure to relatively virulent OI pathogens, such as *Mycobacterium tuberculosis,* that may cause disease early in the course of HIV infection, or lack of access to medical care rather than any inherent difference in the rate of decline of immunologic function.

Readers of this journal will note that many tropical diseases most often featured in the journal's pages–malaria, schistosomiasis, filariasis, onchocerciasis, yellow fever, and dengue, to name a few–have not been implicated as OIs in the AIDS epidemic. Malaria[6,7] and African trypanosomiasis[8,9] have been specifically studied, and HIV infection did not appear to increase the frequency or severity of these diseases. However, interactions between malaria and HIV have been reported: among pregnant women, malaria parasitemia and placental infection rates were higher in HIV-positive than in HIV-negative women, and infants born to HIV-positive women had higher rates of umbilical cord blood parasitemia.[10] As mentioned in the section on Latin America and the Caribbean basin below, South American trypanosomiasis (Chagas' disease) and various forms of leishmaniasis may be more severe in HIV-infected persons. Other tropical infections have been less well studied, and future investigations may indicate adverse effects of HIV infection on the natural history of some of these diseases. Conversely, it is possible that some of these infections may accelerate the course of HIV infection, as has been suggested for TB[11,12] and herpes simplex virus infection.[13,14]

Opportunistic infections of importance in sub-Saharan Africa. The best information on the spectrum of OIs associated with HIV infection in sub-Saharan Africa has come from cross-sectional studies of hospitalized patients that used a standardized diagnostic approach and from autopsy studies.[15–19] Studies of HIV-infected hospitalized patients in Nairobi, Kenya[15] and in Abidjan, Cote d'Ivoire[16] have demonstrated rates of bacteremia (or fungemia) of 26% and 17%, respectively. The organisms most commonly isolated were nontyphoid *Salmonella* species, *S. pneumoniae,* mycobacteria of the *M. tuberculosis* complex, and *C. neoformans* (Table 1). Pyomyositis occurs rarely but is more frequent among HIV-infected than HIV-negative persons, suggesting that deep infections with *Staphylococcus aureus* are also associated with HIV.[20]

Certain clinical syndromes are common in HIV-infected persons in sub-Saharan Africa, including chronic diarrhea, wasting (slim disease), chronic fever without an obvious localizing source, and pulmonary disease.[21]

Diarrhea lasting longer than one month occurs among up to half of patients with AIDS in Africa and seems more frequent than among HIV-infected persons in industrialized countries. The diarrhea is usually intermittent, is not associated with blood or mucus, and is only rarely secretory in nature. In one-third to two-thirds of patients with diarrhea in Uganda, Zaire, and Zambia, no cause was found despite detailed examination.[22–24] Cryptosporidiosis has been reported in 22–48% of patients, isosporiasis in 7–16%, and, in a recent study from Zambia, microsporidiosis in 23%.[25]

The HIV wasting syndrome (slim disease) is likely to have multiple causes. While diarrhea and malabsorption may contribute, reduced food intake is likely to be a major factor, and other diagnoses are frequent among patients with profound wasting. An autopsy study in Cote d'Ivoire found that 44% of patients dying with the HIV wasting syndrome had disseminated TB, compared with 25% of HIV-infected patients without this syndrome.[26]

The chronic fever syndrome is frequently associated with TB and with nontyphoid salmonellosis.[21]

Investigations of patients with pulmonary disease in Bujumbura, Burundi demonstrated that TB and bacterial pneumonia (thought to be caused mostly by common bacterial respiratory pathogens such as *S. pneumoniae* and *Haemophilus influenzae,* based on clinical response to ampicillin) were important causes.[27]

Autopsy studies have been particularly useful in defining the spectrum of OIs associated with HIV infection in sub-Saharan Africa.[18,19] In a large sample of patients dying with HIV disease in Abidjan,[18] TB was present in more than half of those who had one or more diseases fulfilling the Centers for Disease Control and Prevention (CDC) (Atlanta, GA) AIDS surveillance case definition[28] and was responsible for 32% of deaths (Table 2). Bacteremia was considered the cause of death in 11% of patients, and cerebral toxoplasmosis in 10%. These three diseases, therefore, accounted for more than half of all deaths. The importance of TB was demonstrated in another autopsy study among patients dying with pulmonary disease in Abidjan: 40% of the HIV-positive patients died of TB, compared with only 4% of HIV-negative persons.[19]

Several diseases common among patients with AIDS in industrialized countries have been documented less frequently in patients in sub-Saharan Africa; these include PCP, dis-

TABLE 3

Prevalence of opportunistic infections among patients with acquired immunodeficiency syndrome (AIDS) from Brazil and Mexico*

		Mexico—clinical series		Mexico—autopsy studies	
	Brazil surveillance (n = 54,009)†	Volkow and others[41] (n = 39)‡	Vokow and others[41] (n = 107)‡	Mohar and others[42] (n = 177)	Jessurun and others[43] (n = 58)
Candidiasis§	43%	72%	65%	8%	–
Pneumocystis carinii pneumonia	29%	21%	22%	24%	24%
Tuberculosis (TB), pulmonary and extrapulmonary	17%¶	18%#	30%#	25%	28%
Toxoplasmosis, central nervous system	13%	5%	8%	17%	17%
Herpes simplex virus disease	7%	14%	22%	8%	–
Kaposi's sarcoma	6%	0%	47%	30%	41%
Cryptococcosis	5%	8%	12%	11%	7%
Cytomegalovirus disease (CMV)	3%	–	34%	69%**	65%**
Histoplasmosis	2%	0%	4%	10%	5%
Cryptosporidiosis	3%	25%	25%	7%	–
Mycobacterium avium complex (MAC) or other non-TB mycobacterium	2%	–	–	6%††	5%
Aspergillosis	–	–	–	3%	7%
Isosporiasis	2%	8%	8%	1%	–
Coccidioidomycosis	<1%	3%	0%	–	–
Nocardiosis	–	–	–	1%	3%

* – = information unavailable.
† National AIDS surveillance data—opportunistic infections at time of AIDS diagnosis. Source: AIDS Epidemiological Bulletin, Ministry of Health (Brazil) July 27–31, 1994.
‡ Medical record review of patients with AIDS (39 infected from contaminated blood and 107 infected sexually) admitted to three hospitals in Mexico City from 1987 to 1990.
§ Esophageal, tracheal, broncheal, or pulmonary candidiasis.
¶ Disseminated/extrapulmonary only.
# Did not differentiate between *Mycobacterium* species.
** CMV reported as infection; disease was not specified.
†† MAC only.

seminated MAC infection, and CMV disease.[18, 29] In Abidjan, PCP accounted for only 8% of deaths from HIV-associated pulmonary disease[19] and only 2% of all HIV-associated deaths.[18] A recent report from Zimbabwe illustrated that applying clinical criteria to patients with abnormal chest radiographs can identify subgroups of patients in whom the prevalence of PCP is considerably higher than in non-HIV-infected patients, but even in such groups TB remained the most frequent OI.[30] In contrast to the relative rarity of PCP in adults, PCP has been shown to be an important cause of death among HIV-infected infants in Cote d'Ivoire,[31] occurring with a frequency similar to that in HIV-infected infants in industrialized countries.

In Kenya, 14 (29%) of 48 patients hospitalized with advanced HIV disease had mycobacteremia, which was due to *M. tuberculosis* infection in 11 cases and to MAC infection in only three.[29] A study of 50 patients with advanced HIV disease in Uganda detected no cases of MAC bacteremia.[32] Because disease due to MAC and CMV typically occurs late in the course of immune deficiency, when CD4+ lymphocyte counts are < 50 cells/μl, it is possible that many African patients infected with HIV do not survive long enough for these infections to develop.

Regional variations in the frequencies of OIs exist within Africa but have not been adequately documented. Cryptococcosis accounted for only 2% of AIDS deaths in Abidjan,[18] but it is probably more common in central and parts of southern Africa. Mycobacterial infections other than TB (e.g., with *M. kansasii* and *M. avium*) have been longstanding health problems among miners in South Africa and may now be emerging as HIV-associated infections in that population (Churchyard G, unpublished data). Endemic Kaposi's sarcoma (KS) has a striking geographic distribution, being most common in central Africa;[33] HIV-associated KS is likely to have a similar heterogeneous disease frequency, although the incidence of KS has increased in all countries in which HIV disease occurs. Kaposi's sarcoma has recently been associated with a new human herpesvirus, Kaposi's sarcoma-associated herpesvirus or human herpesvirus 8;[34, 35] the epidemiology of this virus infection and its distribution in sub-Saharan Africa are presently unknown.

Some data are available concerning the level of immunosuppression at which various diseases occur in African patients. Median CD4+ lymphocyte counts in HIV-infected patients with newly diagnosed TB have ranged from 198 to 317 cells/μl; counts are somewhat higher among those with pulmonary than with extrapulmonary disease.[36–38] Limited data on other bacterial infections suggest that first episodes of pneumococcal disease are associated with median CD4+ lymphocyte counts in the range of 200–350 cells/μl.[39] Median counts at which these diseases develop in U.S. patients are somewhat lower–approximately 100 CD4+ lymphocytes/μl.[2] However, given the advanced stage of immunodeficiency (median CD4+ lymphocyte count < 90 cells/μl) documented in most patients initially seeking treatment for HIV infection at hospitals in Abidjan,[18] it seems likely that many African patients, like those in industrialized countries, do not have severe OIs until they are severely immunocompromised.

Opportunistic infections of importance in Latin America and the Caribbean basin. As in sub-Saharan Africa, the best information concerning the clinical spectrum of HIV infection in Latin America has been derived from studies of hospitalized patients in advanced stages of immunodeficiency or from autopsy studies (Table 3); such information suggests several similarities and differences in the spectrum of OIs in Latin America and the United States.[40–43]

Tuberculosis appears to be much more common as an OI in Latin America than in the United States and Europe. Disseminated TB was found at autopsy in 25% of Mexican pa-

TABLE 4

Prevalence of opportunistic infections among patients with acquired immunodeficiency syndrome (AIDS)* from Thailand and India (n = number of patients)

	Chiang Mai, Thailand[82] (n = 307)†	Bangkok, Thailand (n = 90)†	Northern Thailand[76] (n = 52)†	Vellore, India[74] (n = 19)‡
Tuberculosis (TB), pulmonary and extrapulmonary	31%	54%	23%§	68%
Cryptococcosis	24%	13%	44%	5%
Pneumocystis carinii pneumonia	13%	7%	25%	–
Penicillium marneffei infection	16%	4%	–	–
Oropharyngeal candidiasis	–	–	–	58%
Esophageal candidiasis	4%	3%	–	–
Toxoplasmosis, central nervous system	7%	–	8%	–
Cryptosporidiosis	5%	–	–	11%
Herpes simplex virus disease	2%	–	–	–
Histoplasmosis	<2%	–	–	–
Cytomegalovirus disease	<1%	2%¶	–	–

* – = information unavailable.
† Patients with AIDS seen in hospitals. Data from Bangkok obtained from S. Tansuphaswadikul and others, International Conference on AIDS, Amsterdam, The Netherlands, 1992.
‡ First 19 AIDS patients seen in a hospital.
§ 10 cases of pulmonary TB, two cases of TB meningitis.
¶ Cytomegalovirus retinitis only.

tients with AIDS[42] compared with 6% of U.S.[44] and 5% of Italian patients.[45] This observation is consistent with the higher incidence of pulmonary TB in Latin America than in the United States, as well as with the elevated incidence of TB among foreign-born persons of Latin American descent in the United States.[42, 46–50]

Other OIs that appear to be more common among HIV-infected persons in Latin America than in North America are cerebral toxoplasmosis,[40, 42, 43] cryptosporidiosis,[51–55] and isosporiasis[40] (Table 3). Since cerebral toxoplasmosis is thought to represent reactivation of latent infection,[56] the higher prevalence of this disease among Latin American patients is consistent with the higher underlying prevalence of *Toxoplasma* infection in Latin America.[57, 58] Isosporiasis is reported in as many as 5% of patients with AIDS in Haiti[59] and 10% of those in Rio de Janeiro, Brazil,[60] compared with about 0.2% of patients with AIDS in the United States.[50] Reports have also shown that the risk of isosporiasis among U.S. residents with AIDS is higher among those born in Latin America and Haiti than among those born in the United States.[50, 59, 61]

The OIs common among patients with AIDS in the United States, such as PCP,[42, 43] oral and esophageal candidiasis,[40] KS,[42, 43] cryptococcosis,[62] and CMV infections,[41–43] appear to be common in Latin America as well (Table 3). Although MAC disease has not been commonly reported as an OI in parts of Latin America, including Brazil, MAC was cultured from the bone marrow of 23 (18%) of 125 patients with AIDS in a hospital in Sao Paulo, Brazil.[63] Therefore, MAC infection may be a more important OI in this region than previously realized.

Several infections endemic to specific parts of Latin America have also been reported in association with HIV disease. *Trypanosoma cruzi*, the cause of Chagas' disease, infects millions of people in Latin America. Reports from Argentina, Brazil, and Chile have described clinical and laboratory findings in about two dozen patients coinfected with HIV and *T. cruzi*.[64–66] These reports suggest that Chagas' disease may result from reactivation of latent *T. cruzi* infection, and that clinical manifestations such as meningoencephalitis may be more frequent and severe in HIV-infected persons. Similarly, cases of cutaneous and visceral leishmaniasis have been described with unusual and more severe clinical manifestations, such as a more chronic relapsing course and higher mortality, in HIV-infected persons in Latin America[67, 68] and elsewhere.[69] Other diseases that have been reported in association with HIV infection include disseminated strongyloidiasis,[70] paracoccidioidomycosis,[71] and disseminated scabies infestation.[72] Additional information will be needed to clarify the extent to which these and other infections occur with increased frequency or severity in HIV-infected persons.

Opportunistic infections of importance in Asia. Less information is available on OIs among HIV-infected persons in Asia than in other parts of the world. Widespread transmission of HIV began later in Asia than in Africa or Latin America. Asia and the Pacific Basin include highly heterogeneous regions and populations, and since this region has only recently been affected by the HIV pandemic, information concerning OIs has only begun to emerge. In addition, of the few reports of OIs in Asia, some are written in Asian languages and are not easily accessible to us for review.

Despite these limitations, the information that is available from Asia suggests that, as in Africa and Latin America, TB is the most common OI in HIV-infected persons;[73–76] these observations are supported by the more frequent reporting of TB as an AIDS-defining illness among Asian-born than among U.S.-born patients in the United States (CDC surveillance data, unpublished). Opportunistic infections commonly reported in other parts of the world, such as PCP,[76–79] herpes simplex virus disease,[80] herpes zoster,[81] oral and esophageal candidiasis,[74, 82, 83] cryptococcosis,[84, 85] and cerebral toxoplasmosis,[76, 82] have also been reported from Asia (Table 4), although reports from a small number of sites suggest a lower prevalence of PCP.[74, 76, 82, 86] However, in the first report of this disease in AIDS patients in India, the authors acknowledge that technical problems in demonstrating the presence of *Pn. carinii* may be a limiting factor in the diagnosis of PCP in that country.[77]

A fungal pathogen that has achieved some notoriety in Southeast Asia is *Penicillium marneffei*, a dimorphic fungus found in several countries in this region.[87] Before the HIV epidemic, disseminated *P. marneffei* infection was observed occasionally in immunocompromised patients in Thailand.[88] However, with the advent of the AIDS epidemic, disseminated *P. marneffei* infection, characterized by fever, anemia, weight loss, and generalized papular skin lesions, has become an important cause of HIV-associated disease in Thailand and elsewhere in Southeast Asia.[89–93] In fact, in northern Thailand, disseminated *P. marneffei* infection has become the third most common OI associated with HIV disease, after TB and cryptococcal meningitis.[87] In addition to endemic cases, travelers from regions where *P. marneffei* is not endemic have become infected with *P. marneffei* while traveling in Southeast Asia.[94, 95]

PREVENTION OF OIS

As indicated in the USPHS/IDSA Guidelines, prevention of OIs among patients with HIV infection entails measures to prevent exposure to opportunistic pathogens in the environment, chemoprophylaxis and vaccination to prevent an initial episode of disease, and chemoprophylaxis to prevent disease recurrence.

Possible measures to prevent exposure to opportunistic pathogens depend not only on the spectrum of OIs in a given region, but also on knowledge concerning the source of these pathogens in the environment. Environmental sources of some opportunistic pathogens in the developing world may be quite different from the sources of pathogens in North America (e.g., moldy sugar cane or bamboo has been suggested as a possible source of *P. marneffei* infection in Thailand).[90] For others, sources can be expected to be similar (e.g., unpasteurized dairy products and raw or undercooked eggs, meat, poultry, or fish as sources of *Salmonella* infection, and undercooked meat as a source of *Toxoplasma* infection). For many opportunistic pathogens, environmental sources may be unknown, as is often the case in North America.

When environmental sources are known, persons formulating recommendations to prevent exposures must consider their feasibility and their impact on the quality of life. Avoiding a pathogen that is ubiquitous in the environment or intimately associated with a person's home environment or daily activities may be impractical. However, some measures that may prove useful include avoiding contact with patients with TB, such as in health care settings, and avoiding unpasteurized dairy products and raw or undercooked foods that pose a risk of *Salmonella* or *Toxoplasma* infection.

Similarly, several measures to prevent disease by chemoprophylaxis or vaccination in the industrialized world may be applicable in resource-poor countries. Three such measures recommended in the USPHS/IDSA guidelines for use in North America–TMP/SMX, INH, and vaccination against *S. pneumoniae*–are relatively inexpensive and may offer possibilities for preventing OIs in the developing world.

Trimethoprim-sulfamethoxazole is effective against PCP, which is an infrequent cause of disease in sub-Saharan Africa but seems more common in Latin America and Southeast Asia. Studies in industrialized countries have shown TMP/SMX to be effective in reducing the incidence of PCP and in prolonging survival.[96–99] This drug combination is also protective against cerebral toxoplasmosis[4] and possibly against various bacterial infections, such as those caused by *S. pneumoniae*,[100] *Salmonella* species, and *Nocardia*, some of which are more common among persons with AIDS in developing countries than in the United States. The recommended dose of this drug for immunocompromised patients–one double-strength tablet daily–costs only about $60 U.S. per year.[3] Obstacles to the use of this drug in resource-poor settings include cost (which although generally affordable in the United States may be significant in developing countries), toxicity, adherence to prophylaxis, and the emergence of drug resistance. A placebo-controlled trial of the influence of TMP/SMX on survival was begun in 1996 in Cote d'Ivoire among HIV-infected patients with TB, whose high rates of mortality may result from other potentially preventable HIV-associated diseases.[101] Assessment of TMP/SMX is also planned in South Africa. Results of these studies should shed light on the value of TMP/SMX in preventing disease and death from OIs in the developing world.

An additional issue regarding the use of TMP/SMX is when to begin chemoprophylaxis. Initiation of chemoprophylaxis against PCP in North America is guided by the results of regular monitoring of the CD4+ lymphocyte count. However, CD4+ monitoring by flow cytometry is not possible in resource-poor settings. Simplified methods for CD4+ testing have been developed for use in developing countries,[102] but even these methods are not widely feasible at present in the least developed countries. A more practical approach to assessing HIV-related immunosuppression and the risk of OIs is based upon staging systems that use clinical and more widely available laboratory criteria. A World Health Organization Staging System for HIV Infection and Disease was prepared by an international collaborating group[103] and modified by others to include results of laboratory tests, such as absolute lymphocyte count, hematocrit, and erythrocyte sedimentation rate.[104–107] These modified staging systems correlated reasonably well with CD4+ counts < 200 cells/μl in a cross-sectional study in Brazil[106] and with survival in a cohort study in Rwanda[107] and may prove useful in selecting HIV-infected persons likely to benefit from chemoprophylaxis with TMP/SMX.

Isoniazid is of proven efficacy in preventing TB in HIV-infected persons and in one study was shown to prolong survival.[108] The USPHS/IDSA guidelines recommend tuberculin skin testing soon after diagnosis of HIV infection and initiation of INH prophylaxis for those with a positive tuberculin skin test (TST) result (5 mm of induration in this population).[4] Late detection of HIV infection, which often occurs in developing countries, could result in a high frequency of TST anergy. Conversely, in settings where children receive bacillus Calmette-Guerin (BCG) vaccination, some proportion of positive TSTs in HIV-positive children or even in adults might reflect the residual effect of BCG vaccine rather than prior infection with *M. tuberculosis*. Thus, in developing countries, as in industrialized countries, it may be reasonable to recommend that INH prophylaxis be considered for all HIV-infected persons from populations with a high prevalence of *M. tuberculosis* infection. The World Health Organization and the International Union Against Tuberculosis and Lung Disease have recommended that INH be given for 6–12 months to HIV-infected persons without active TB in these settings.[109] The cost of this drug is about $60 U.S. per year.[3] However, as with TMP/SMX, administration of INH in the developing world is not as straightforward as in the United States. In addition to cost, potential problems include toxicity, difficulty in excluding active TB before initiating chemoprophylaxis, danger of promoting INH resistance when active TB is not excluded, and low adherence to prophylaxis. Additionally, in regions in which the prevalence of *M. tuberculosis* infection and the risk of reinfection are high, chemoprophylaxis may have to be lifelong to be effective.

At least four placebo-controlled trials of preventive therapy with INH, started before the international recommendations were issued, continue in Kenya, Uganda, Zambia, and Thailand.[110] Studies of different prophylactic regimens for TB, such as rifampicin plus pyrazinamide, are ongoing or planned in different parts of the world.

Streptococcus pneumoniae is a major cause of pneumonia and sepsis in HIV-infected patients in the developing world. The 23-valent pneumococcal polysaccharide vaccine, which costs only about $10 per dose,[3] is of proven benefit in immunocompetent persons and would be expected to be of some benefit in HIV-infected persons, although efficacy data are lacking. Late detection of HIV infection in developing countries could result in decreased efficacy of pneumococcal vaccination. A placebo-controlled study of pneumococcal vaccine in persons with HIV infection has begun in Uganda, and studies may be initiated in other countries such as South Africa.

Although fluconazole has been shown to reduce the incidence of candidiasis and cryptococcal disease,[111] primary prophylaxis against fungal infections is expensive and not generally recommended, even in the United States.[4] However, this intervention may merit consideration in areas with unusually high incidence of diseases such as cryptococcosis and *P. marneffei* infection.

RESEARCH PRIORITIES

Continued research on the prevention of OIs in resource-poor countries will require an integrated approach, including identification of HIV infection; documentation of the spectrum of disease in different regions; determination of environmental sources of opportunistic pathogens and ways to reduce exposure; assessment of chemoprophylaxis and vaccination against specific OIs; and evaluation of inexpensive alternatives to CD4+ lymphocyte quantitation for triggering initiation of chemoprophylaxis.

The observation that HIV infection is often not diagnosed in the developing world until the patient is in an advanced stage of immunodeficiency indicates that limited survival benefit will come from investing in the treatment of patients hospitalized with HIV disease, and that extending healthy life will require identifying HIV infection earlier in its course. Ideally, patients should be identified as HIV-infected as early as possible, not only so that measures to prevent OIs can be instituted, but also so that patients can be counseled concerning preventing transmission of HIV to others. Although screening services for the general public are scarce in many resource-poor countries, opportunities may exist for the delivery of health care interventions for HIV/AIDS through industrial and occupational health schemes, and these need to be explored.

The spectrum of OIs and the stages of HIV disease at which they occur should be ascertained in well-defined populations in different regions using standardized diagnostic techniques. Environmental sources of opportunistic pathogens in various regions need to be determined where not yet defined so that behavioral interventions likely to reduce exposure to infection can be developed and evaluated. Risk factors for acquiring TB should be explored, including exposure to patients with TB in health care settings. Additional interventions that are relevant and merit study include avoiding unpasteurized dairy products and undercooked meat, poultry, and fish to prevent salmonellosis and toxoplasmosis, and boiling drinking water to avoid diarrheal diseases such as cryptosporidiosis.

The chemoprophylactic interventions described above should be assessed in terms of their efficacy, toxicity, cost-effectiveness, and impact on survival; the potential for the development of drug resistance; and the likelihood that patients will adhere to their prophylactic regimens. For TB, research priorities concerning preventive therapy for TB have been recently discussed.[110, 112] The duration of preventive treatment (which may need to be life-long) and the need for preventive therapy after successful treatment of TB disease need to be assessed. The ideal management of persons who are anergic must be determined. At least as important are operational factors related to the delivery of preventive therapy and assurance of adherence; directly observed preventive therapy for TB may need to be considered.

Although these different prophylactic interventions need to be assessed individually, there is also a need to design and evaluate an intervention package comprising a combination of all or some of the possible interventions described. The nature of this package will depend on the spectrum of OIs, the possible interventions, and the resources available in each locale. Ideally, each region should develop its own approach to prevention of OIs, as has been done for U.S. patients in the USPHS/IDSA guidelines. Such an effort has already been undertaken for Latin American and the Caribbean basin.

A program to prevent OIs must also be viewed in terms of the total resources available for treatment of HIV infection. Guidelines for management of AIDS-associated syndromes and diseases have been published,[113] but standards of care for persons with HIV/AIDS in resource-poor countries need to be further defined and promulgated. These should include standardized approaches to prevention of OIs, indications for hospitalization, and lists of essential drugs, including those for palliation and terminal care. Such guidelines could conceivably include different levels of care, depending on the resources available in the settings in which they will be implemented.

Finally, the prevention of OIs, and the care of HIV-infected persons in general, must be viewed in terms of other health priorities facing resource-poor nations. Such countries already struggle to respond to other infectious diseases, such as diarrheal and respiratory diseases, malaria, yellow fever, dengue, schistosomiasis, and filariasis. With such competing priorities and inadequate resources, some may argue that extending the lives of HIV-infected persons by a few years is not a high priority in these nations. However, HIV-infected persons are generally in the most productive years of their lives, and extension of life is likely to have economic as well as humanitarian benefits. Many have young children who will struggle to survive when one or both parents are deceased. Prevention of TB in HIV-infected persons can be expected to reduce the impact of this disease in non-HIV-infected populations in these areas as well. Furthermore, a basic standard of care for HIV-infected persons in developing countries is likely to involve interventions, such as TMP/SMX, INH, and pneumococcal vaccination, which are relatively inexpensive even for resource-poor nations. One thing is certain: the need for health services to accommodate

HIV-infected patients who seek care will continue to grow. Clinicians, epidemiologists, researchers, and public health officials in these regions must recognize that HIV infection now presents a challenge as important as those of other, long-recognized diseases that have traditionally been the focus of medical professionals in tropical regions.

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